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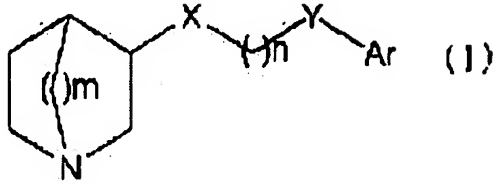
(54) 1-AZABICYCLOALKANE COMPOUND AND PHARMACEUTICAL USE THEREOF

(57)Abstract:

PROBLEM TO BE SOLVED: To provide a new compound having α7-nicotine receptor agonism or α7-nicotine receptor partial agonism, therefore useful as a therapeutic or prophylactic agent for such diseases as Alzheimer's disease, recognition dysfunction, attention-defective hyperkinesia, anxiety, depression, schizophrenia, epilepsy, pain, Tourette's syndrome, Parkinson's disease and Huntington's disease.

SOLUTION: This new compound is an 1-azabicycloalkane compound of the general formula (I) (wherein, the definitions of the respective symbols are such as to be described in the specification), an optical isomer thereof or a pharmaceutically acceptable salt



(I)

thereof.

LEGAL STATUS

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[Date of final disposal for application]

[Patent number]

[Date of registration]

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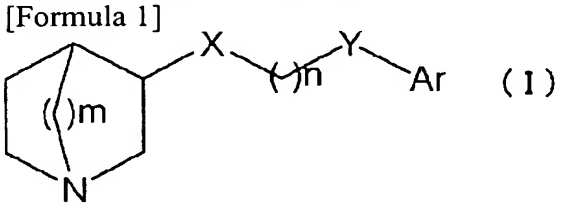
* NOTICES *

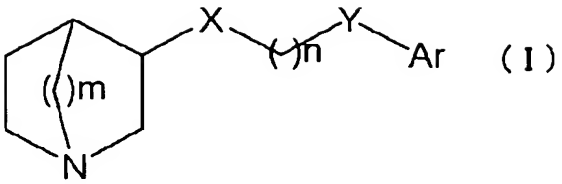
1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] General formula (I)
[Formula 1]



(Among a formula, X does not exist or shows O, S, or NH.) Y shows CH2 or C=O. m shows 1 or 2. n shows the integer of 0, or 1-3. Ar shows the naphthyl group which may have the 2 ring type aromatic series heterocycle which may have the substituent, or a substituent. Salt which can be permitted on 1-azabicyclo alkane compound expressed, its optical isomer, or its physic.
[Claim 2] The salt which can be permitted on 1-azabicyclo alkane compound according to claim 1 whose 2 ring type aromatic series heterocycle is benzothiophene, benzofuran, benzothiazole, or benzimidazole, its optical isomer, or its physic.
[Claim 3] The salt which can be permitted on 1-azabicyclo alkane compound according to claim 1 chosen from the following compounds, its optical isomer, or its physic.
(1) 3- () ([Benzo b] thiophene-2-IRU) methoxy-1-azabicyclo [2.2.2] octane (2) (R)-3-([Benzo b] thiophene-2-IRU) (methoxy)-1-azabicyclo [2.2.2] octane (3) (S)-3 - () Methoxy-1-azabicyclo [2.2.2] octane (4)3-([Benzo b] thiophene-3-IRU) (methoxy)-1-azabicyclo [2.2.2] octane ([Benzo b] thiophene-2-IRU) (5) 3- () (2-naphthyl) Methoxy-1-azabicyclo [2.2.2] octane (6)3-(1-naphthyl) (methoxy)-1-azabicyclo [2.2.2] octane (7) 3 - (2- ()) [[Benzo b] thiophene] - two - IRU -- ethyl - one - azabicyclo -- [-- 2.2.2 --] -- an octane -- (-- eight --) -- (-- + --) - three - (2-([Benzo b] thiophene-2-IRU) ethyl) - one - azabicyclo -- [-- 2.2.2 --] -- an octane -- (9) (-) -3- () [2-] 1-azabicyclo [2.2.2] octane (11) ([Benzo b] thiophene-2-IRU) ethyl-1-azabicyclo [2.2.2] octane (10) 3-(2-([Benzo b] thiophene-2-IRU)-2-oxo-ethyl)- (+) -3- () [2-] (-- benzo -- [-- b --] -- a thiophene - two - IRU --) - two - oxo-one -- ethyl - one - azabicyclo -- [-- 2.2.2 --] -- an octane -- (-- 12 --) -- (-) - three - (2-([Benzo b] thiophene-2-IRU)-2-oxo-ethyl) - one - azabicyclo -- [-- 2.2.2 --] -- an octane -- (13) 3- () [2-] (Benzothiazole-2-IRU)-2-oxo-ethyl-1-azabicyclo [2.2.2] octane (14) 3-(2-(1-methyl benzimidazole-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane (15) 3- () [2-] ([Benzo b] furan-2-IRU)-2-oxo-ethyl-1-azabicyclo [2.2.2] octane (16) 3-([Benzo b] thiophene-2-IRU) (methyl)-1-azabicyclo [2.2.2] octane (17) 3 - () Carbonyl-1-azabicyclo [2.2.2] octane (18) 3-(3-([Benzo b] thiophene-2-IRU) propyl)-1-azabicyclo [2.2.2] octane (19) 3-([Benzo b] thiophene-2-IRU) (3-([Benzo b] thiophene-2-IRU)-3-oxo-propyl)-1-azabicyclo [2.2.2] octane [claim 4] General formula (I)
[Formula 2]

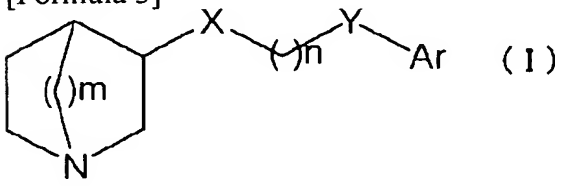


(I)

(Among a formula, X does not exist or shows O, S, or NH.) Y shows CH2 or C=O. m shows 1 or 2. n shows the integer of 0, or 1-3. Ar shows the naphthyl group which may have the 2 ring type aromatic series heterocycle which may have the substituent, or a substituent. Ligand of alpha7 nicotinic receptor which consists of a salt which can be permitted on 1-azabicyclo alkane compound expressed, its optical isomer, or its physic.

[Claim 5] General formula (I)

[Formula 3]

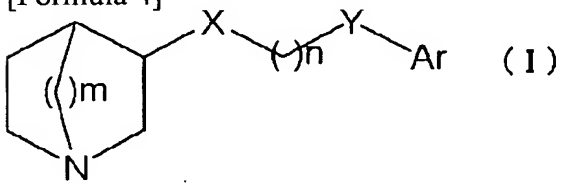


(I)

(Among a formula, X does not exist or shows O, S, or NH.) Y shows CH2 or C=O. m shows 1 or 2. n shows the integer of 0, or 1-3. Ar shows the naphthyl group which may have the 2 ring type aromatic series heterocycle which may have the substituent, or a substituent. alpha7 nicotinic-receptor agonist or alpha7 nicotinic-receptor partial agonist which consists of a salt which can be permitted on 1-azabicyclo alkane compound expressed, its optical isomer, or its physic.

[Claim 6] General formula (I)

[Formula 4]

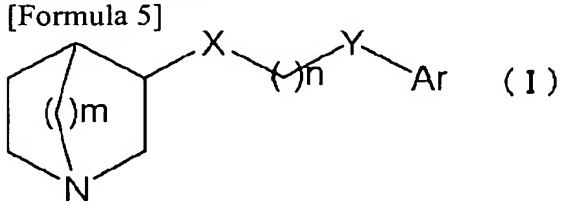


(I)

(Among a formula, X does not exist or shows O, S, or NH.) Y shows CH2 or C=O. m shows 1 or 2. n shows the integer of 0, or 1-3. Ar shows the naphthyl group which may have the 2 ring type aromatic series heterocycle which may have the substituent, or a substituent. Cognitive failure improvement medicine which consists of a salt which can be permitted on 1-azabicyclo alkane compound expressed, its optical isomer, or its physic.

[Claim 7] General formula (I)

[Formula 5]

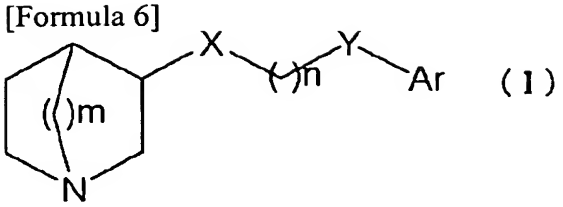


(I)

(Among a formula, X does not exist or shows O, S, or NH.) Y shows CH2 or C=O. m shows 1 or 2. n shows the integer of 0, or 1-3. Ar shows the naphthyl group which may have the 2 ring type aromatic series heterocycle which may have the substituent, or a substituent. Anti-dementia medicine which consists of a salt which can be permitted on 1-azabicyclo alkane compound expressed, its optical isomer, or its physic.

[Claim 8] General formula (I)

[Formula 6]

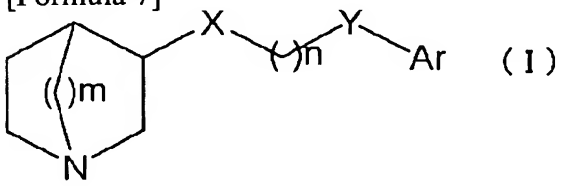


(I)

(Among a formula, X does not exist or shows O, S, or NH.) Y shows CH2 or C=O. m shows 1 or 2. n shows the integer of 0, or 1-3. Ar shows the naphthyl group which may have the 2 ring type aromatic series heterocycle which may have the substituent, or a substituent. Schizophrenia remedy which consists of a salt which can be permitted on 1-azabicyclo alkane compound expressed, its optical isomer, or its physic.

[Claim 9] General formula (I)

[Formula 7]

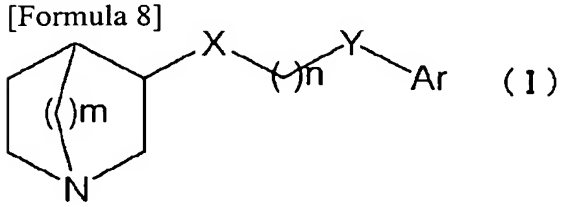


(I)

(Among a formula, X does not exist or shows O, S, or NH.) Y shows CH2 or C=O. m shows 1 or 2. n shows the integer of 0, or 1-3. Ar shows the naphthyl group which may have the 2 ring type aromatic series heterocycle which may have the substituent, or a substituent. Electronegative symptom improvement medicine of schizophrenia which consists of a salt which can be permitted on 1-azabicyclo alkane compound expressed, its optical isomer, or its physic.

[Claim 10] General formula (I)

[Formula 8]

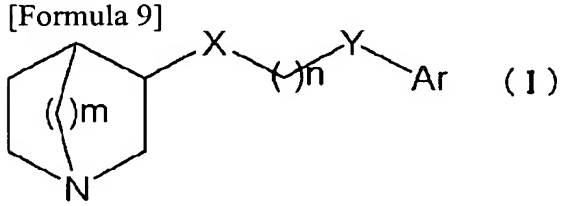


(I)

(Among a formula, X does not exist or shows O, S, or NH.) Y shows CH2 or C=O. m shows 1 or 2. n shows the integer of 0, or 1-3. Ar shows the naphthyl group which may have the 2 ring type aromatic series heterocycle which may have the substituent, or a substituent. Attention deficit hyperactivity disorder remedy which consists of a salt which can be permitted on 1-azabicyclo alkane compound expressed, its optical isomer, or its physic.

[Claim 11] General formula (I)

[Formula 9]



(I)

(Among a formula, X does not exist or shows O, S, or NH.) Y shows CH2 or C=O. m shows 1 or 2. n shows the integer of 0, or 1-3. Ar shows the naphthyl group which may have the 2 ring type aromatic series heterocycle which may have the substituent, or a substituent. Alzheimer disease remedy which consists of a salt which can be permitted on 1-azabicyclo alkane compound expressed, its optical isomer, or its physic.

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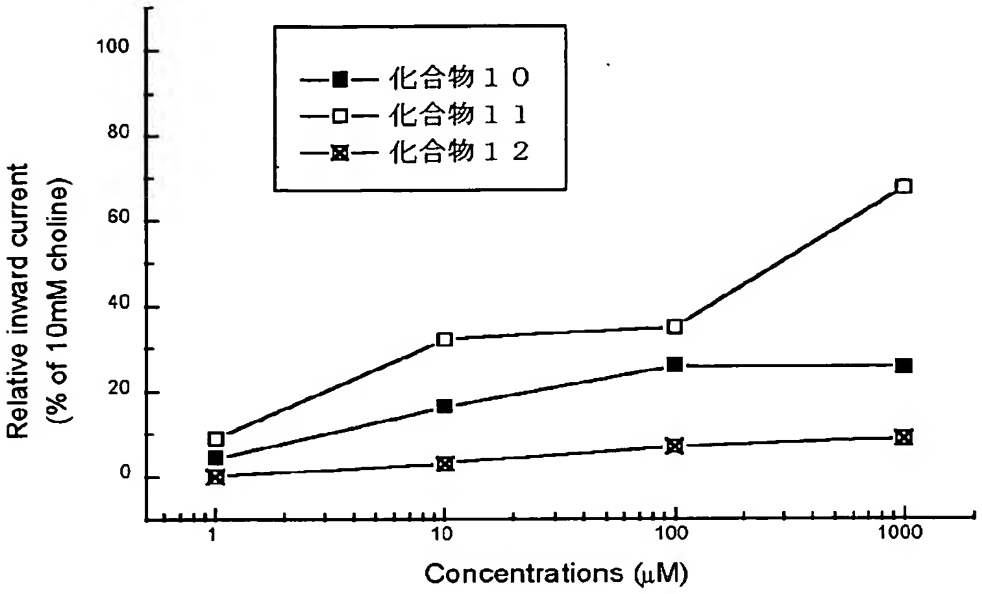
Drawing selection drawing 1



[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the new 1-azabicyclo alkane compound for providing the disease of a central nervous system with useful physic.
[0002]
[Description of the Prior Art] It is known that many subtypes exist and, as for the nicotinic receptor, at least 11 subtypes (alpha2-9 and beta2-4) are identified by current (237 total theory: Trends in Pharmacological Sciences, 12:34-40, 1991; Progress in Neurobiology, 53:199- 1997). A nicotinic receptor exists as a pentamer of these subtypes, an ion channel is formed, and taking in calcium ion etc. to intracellular is known. In the brain, although it is known that two kinds of subtypes (alpha4beta2 and alpha7) mainly exist, alpha4beta2 nicotinic receptor is formed as hetero oligomer of alpha4 subunit and beta2 subunit, and alpha7 nicotinic receptor is formed as gay oligomer of alpha7 subunit. Moreover, these subtypes (alpha4beta2 nicotinic receptor and alpha7 nicotinic receptor) are distributed over the broad parts within a brain (the cerebral cortex, hippocampus, etc.). It is known that the nicotinic receptor (alpha4beta2 nicotinic receptor and alpha7 nicotinic receptor) in a central nervous system is participating in nervous generating and differentiation, study and formation of storage, and the various physiological functions of remuneration (total theory: Brain Research Reviews, 26:198-216, 1998; Trends in Neurosciences, 22:555-561, 1999; MolecularNeurobiology, 20:1-16, 1999). It is known that the nicotinic receptor which exists in a presynapsis has played the important role in emission of various neurotransmitter (acetylcholine, dopamine, glutamic acid, etc.) (total theory: Trends in Pharmacological Sciences, 20:92-98, 1997; Annual Reviews of Neuroscience 22:443-485, 1999; Molecular Neurobiology, 20:1-16, 1999). Moreover, it is known that the nicotinic receptor which exists in a back synapse has played the important role in choline system neural transmission (total theory: Trends in Pharmacological Sciences, 22:555-561, 1999; Molecular Neurobiology, 20:1-16, 1999).
[0003] On the other hand, an acetylcholine system is one of the neurotransmitter with a main central nervous system, having played the role important for accommodation of a nerve activity of the cerebral cortex or a hippocampus is known, and possibility of participating in the symptoms of various kinds of central diseases is pointed out. For example, reduction of the acceptor of a nicotinic receptor (alpha4beta2 nicotinic receptor and alpha7 nicotinic receptor) is reported also in the acetylcholine system by the cerebral cortex and the hippocampus of an autopsy brain of an Alzheimer disease patient (Journal of Neurochemistry, 46:288-293, 1986; Alzheimer's Disease Reviews, 3:20-27, 1998; Alzheimer's Disease Reviews, 3:28-34, 1998). Furthermore, it is reported that the amount of mRNA of alpha7 nicotinic receptor in an Alzheimer disease patient's lymphocyte is increasing intentionally as compared with the amount of mRNA of alpha7 nicotinic receptor a normal person's lymphocyte (36 Alzheimer's Research, 3:29- 1997). Moreover, it is reported that the amount of mRNA of alpha7 nicotinic receptor in an Alzheimer disease patient's hippocampus is increasing intentionally as compared with the amount of mRNA of alpha7 nicotinic receptor a normal person's hippocampus (Molecular Brain Research, 66:94-103, 1999). In this report, it is suggested from the amount of mRNA of other

subtypes (alpha3 and alpha4) not having been accepted for the difference between a normal person's brain, and the patient brain of an Alzheimer disease that alpha7 nicotinic receptor has played the important role in the symptoms of an Alzheimer disease. In the trial using the primary culture system of the rat cerebral cortex, it is reported in neurotoxicity [by the amyloid beta peptide] that nicotine shows a nerve protective action through alpha7 nicotinic receptor (Annuals of Neurology, 42:159-163, 1997). As one of the mechanisms neurotoxicity [by the amyloid beta peptide], there is an oxidization stress theory by radical reaction, and possibility that the stimulus of a nicotinic receptor is adjusting intracellular oxidization stress is suggested. Therefore, alpha7 nicotinic receptor is considered that possibility of being concerned with the cause of a disease of an Alzheimer disease or the site of action as a remedy is high.

[0004] On the other hand, the relation of people with schizophrenia and alpha7 nicotinic receptor attracts attention (total theory: Harvard Reviews of Psychiatry, 2:179-192, 1994; Schizophrenia Bulletin, 22:431-445, 1996; Schizophrenia Bulletin, 24:189-202, 1998; Trends in Neurosciences, 22:555-561, 1999). Moreover, it is reported that the number of alpha7 nicotinic receptors of people's with schizophrenia autopsy brains (a hippocampus, frontal cortex, etc.) is decreasing (Schizophrenia Bulletin, 22:431-445, 1996; Schizophrenia Bulletin, 24:189-202, 1998; NeuroReport, 10:1779-1782, 1999). Moreover, it is reported that the abnormalities of sensory gating observed by people with schizophrenia improve by administration of nicotine and that alpha7 nicotinic receptor is participating in this phenomenon further. Therefore, alpha7 nicotinic receptor is considered that possibility of being concerned with the cause of a disease of schizophrenia is high. By the way, although the mechanism of the symptoms of schizophrenia now is not clear, the assumption to which the neurotransmission system of the glutamic acid which is one of the excitatory amino acid is falling is advocated broadly (total theory: Harvard Reviews of Psychiatry, 3:241-253, 1996; American Journal of Psychiatry, 148:1301-1308, 1991; Archives of General Psychiatry, 52:998-1007, 1995). By emitting the glutamic acid from a presynapsis, the agonist of alpha7 nicotinic receptor activates the neurotransmission system of glutamic acid which is falling, and is considered to improve the symptoms (an electropositive symptom, an electronegative symptom, cognitive dysfunction, etc.) seen by people with schizophrenia. Thus, alpha7 nicotinic receptor is considered that possibility of being concerned with the site of action of the remedy of schizophrenia is high.

[0005] Furthermore, the agonist of alpha7 nicotinic receptor may participate also in control of smoking from alpha7 nicotinic receptor existing also in the reward system considered to participate in dependence of smoking (Trends in Neurosciences, 22:555-561, 1999; NeuroReport, 10:697-702, 1999; Neurosciences, 85:1005-1009, 1998). It is thought that alpha7 nicotinic-receptor agonist or alpha7 nicotinic-receptor partial agonist is more useful than these things as a remedy or prophylactics, such as an Alzheimer disease, cognitive dysfunction, an attention deficit hyperactivity disorder, anxiety, depression, schizophrenia, epilepsy, a pain, tow let syndrome, a Parkinson Mr. disease, and a Huntington disease, and it has the advantage as compared with the compound which is alpha4beta2 nicotinic-receptor agonist. Therefore, agonist or partial agonist alternative to alpha7 nicotinic receptor is desirable. Moreover, since these drugs have the nerve protective action, its cholinergic nerve transfer is useful also as the therapy or prevention of the neurodegenerative disease which has caused abnormalities. Furthermore, it can be used for urging control of smoking.

[0006] As alpha7 nicotinic-receptor partial agonist to precede, 3-[(2, 4-JIMETOSHIKI) benzylidene] ANABASEIN (development code GTS-21:WO 94/05288), as alpha7 nicotinic-receptor agonist -- spiro, although [the 1-azabicyclo [2.2.2] octane -3 and 5 '- oxazolidine -2'-ON] (development code AR-R 17779:WO 96/06098) are known It is known that all have troubles, like brain internal transmigration nature with the weak compatibility to alpha7 acceptor is low. Moreover, although the azabicyclo ester compound of the carbamic acid which is the agonist of alpha7nAChR (alpha7 nicotine acetylcholine receptor) is indicated by WO 97/No. 30998, the compatibility over the acceptor of this compound is not strong to it. Furthermore, 1-azacyclo alkane compound which has compatibility in a muscarinic receptor as structure resemblance of this compound (JP,4-226981,A), The azabicyclo compound as a calcium channel antagonist (****** No. 503463 [seven to] official report), The quinuclidine derivative as a

squalene synthetase inhibitor (****** No. 500098 [eight to], and ****** No. 504803 [eight to]), 3-(2-oxo--2-phenylethyl) quinuclidine and 3-(2-phenylethyl) quinuclidine (Khim.Geterotsikl.Soedin. 1983, the 3rd volume, 381 - 385 pages ()) [Chemical] Abstract, 100:22563w, etc. are known. However, these are not the things [all] aiming at alpha7 nicotinic-receptor agonist.

[0007]

[Problem(s) to be Solved by the Invention] This invention has powerful alpha7 nicotinic-receptor actuation operation or alpha7 nicotinic-receptor partial actuation operation, and it is in offering remedies, such as an Alzheimer disease, cognitive dysfunction, an attention deficit hyperactivity disorder, anxiety, depression, schizophrenia, epilepsy, a pain, tow let syndrome, a Parkinson Mr. disease, and a Huntington disease, or a prophylactic, the remedy of a neurodegenerative disease with which cholinergic nerve transfer has caused abnormalities or a prophylactic, and the still more useful new molecular entity as a non-smoking medicine.

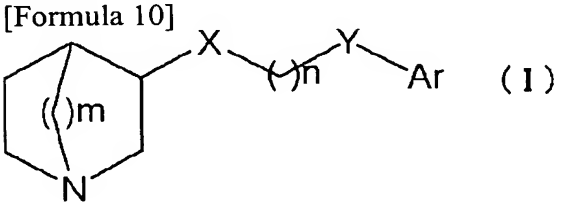
[0008]

[Means for Solving the Problem] this invention persons found out that the salt which can be permitted on 1-azabicyclo alkane compound expressed by the following general formula (I), its optically active substance, or its physic had having alternative and powerful compatibility to alpha7 nicotinic receptor, especially alternative and powerful alpha7 nicotinic-receptor actuation operation, or alpha7 nicotinic-receptor partial actuation operation, as a result of inquiring wholeheartedly. Therefore, it can become useful [this invention compound / as a non-smoking medicine] to remedies, such as an Alzheimer disease, cognitive dysfunction, an attention deficit hyperactivity disorder, anxiety, depression, schizophrenia, epilepsy, a pain, tow let syndrome, a Parkinson Mr. disease, and a Huntington disease, or a prophylactic, the remedy of a neurodegenerative disease with which cholinergic nerve transfer has caused abnormalities or a prophylactic, and a pan. This invention is as follows.

1. General formula (I)

[0009]

[Formula 10]



(I)

[0010] (Among a formula, X does not exist or shows O, S, or NH.) Y shows CH2 or C=O. m shows 1 or 2. n shows the integer of 0, or 1-3. Ar shows the naphthyl group which may have the 2 ring type aromatic series heterocycle which may have the substituent, or a substituent. Salt which can be permitted on 1-azabicyclo alkane compound expressed, its optical isomer, or its physic.

2. Salt which can be permitted on said 1-azabicyclo alkane compound of one publication whose 2 ring type aromatic series heterocycle is benzothiophene, benzofuran, benzothiazole, or benzimidazole, its optical isomer, or its physic.

[0011] 3. Salt which can be permitted on 1-azabicyclo alkane compound of said one publication chosen from the following compounds, its optical isomer, or its physic.

(1) 3- () ([Benzo b] thiophene-2-IRU) methoxy-1-azabicyclo [2.2.2] octane (2) (R)-3-([Benzo b] thiophene-2-IRU) (methoxy)-1-azabicyclo [2.2.2] octane (3) (S)-3 - () Methoxy-1-azabicyclo [2.2.2] octane (4)3-([Benzo b] thiophene-3-IRU) (methoxy)-1-azabicyclo [2.2.2] octane ([Benzo b] thiophene-2-IRU) (5) 3- () (2-naphthyl) Methoxy-1-azabicyclo [2.2.2] octane (6)3-(1-naphthyl) (methoxy)-1-azabicyclo [2.2.2] octane (7) 3 - (2- ()) [[Benzo b] thiophene] - two - IRU -- ethyl - one - azabicyclo -- [-- 2.2.2 --] -- an octane -- (-- eight --) -- (-- + --) - three - (2-([Benzo b] thiophene-2-IRU) ethyl) - one - azabicyclo -- [-- 2.2.2 --] -- an octane -- (9) (-) -3- () [2-] 1-azabicyclo [2.2.2] octane (11) ([Benzo b] thiophene-2-IRU) ethyl-1-azabicyclo [2.2.2] octane (10) 3-(2-([Benzo b] thiophene-2-IRU)-2-oxo-ethyl)- (+) -3- () [2-] (-- benzo -- [-- b --] -- a thiophene - two - IRU --) - two - oxo-one -- ethyl - one - azabicyclo -- [-- 2.2.2 --] -- an octane -- (-- 12 --) -- (-) - three - (2-([Benzo b] thiophene-2-IRU)-2-oxo-

ethyl) - one - azabicyclo -- [-- 2.2.2 --] -- an octane -- (13) 3- () [2-] (Benzothiazole-2-IRU)-2-oxo-ethyl-1-azabicyclo [2.2.2] octane (14) 3-(2-(1-methyl benzimidazole-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane (15) 3- () [2-] ([Benzo b] furan-2-IRU)-2-oxo-ethyl-1-azabicyclo [2.2.2] octane (16) 3-([Benzo b] thiophene-2-IRU) (methyl)-1-azabicyclo [2.2.2] octane (17) 3 - () Carbonyl-1-azabicyclo [2.2.2] octane (18) 3-(3-([Benzo b] thiophene-2-IRU) propyl)-1-azabicyclo [2.2.2] octane (19) 3-([Benzo b] thiophene-2-IRU) (3-([Benzo b] thiophene-2-IRU)-3-oxo-propyl)-1-azabicyclo [2.2.2] octane [0012] 4. Ligand of alpha7 nicotinic receptor which consists of salt which can be permitted on 1-azabicyclo alkane compound of general formula (I), its optical isomer, or its physic.
5. alpha7 nicotinic-receptor agonist or alpha7 nicotinic-receptor partial agonist which consists of salt which can be permitted on 1-azabicyclo alkane compound of general formula (I), its optical isomer, or its physic.
6. Cognitive failure improvement medicine which consists of salt which can be permitted on 1-azabicyclo alkane compound of general formula (I), its optical isomer, or its physic.
7. Anti-dementia medicine which consists of salt which can be permitted on 1-azabicyclo alkane compound of general formula (I), its optical isomer, or its physic.
8. Schizophrenia remedy which consists of salt which can be permitted on 1-azabicyclo alkane compound of general formula (I), its optical isomer, or its physic.
9. Electronegative symptom improvement medicine of schizophrenia which consists of salt which can be permitted on 1-azabicyclo alkane compound of general formula (I), its optical isomer, or its physic.
10. The attention deficit hyperactivity disorder remedy which consists of a salt which can be permitted on 1-azabicyclo alkane compound of a general formula (I), its optical isomer, or its physic.
11. The Alzheimer disease remedy which consists of a salt which can be permitted on 1-azabicyclo alkane compound of a general formula (I), its optical isomer, or its physic.
[0013]
[Embodiment of the Invention] The example of each radical in the above-mentioned general formula (I) is as follows. The structure which the 2 ring type aromatic series heterocycle in Ar shared a part of aromatic series heterocycle, benzene ring, or same or ring of each other [heterocycles / different / aromatic series], and condensed is shown, and benzo KISAZORU, benzothiazole, 1, 2-bends isoxazole, 1, a 2-bends iso thiazole, Indore, 1-benzofuran, 1-benzothiophene, a quinoline, an isoquinoline, quinazoline, etc. are mentioned. Moreover, Ar is combinable with Y from the carbon atom of the arbitration on the ring.
[0014] As a substituent of 2 ring type aromatic series heterocycle, (1) fluorine, chlorine, a bromine, The halogen chosen from iodine, (2) methyls, ethyl, propyl, isopropyl, The alkyl of the carbon numbers 1-4 chosen from butyl, isobutyl, the 3rd class butyl, etc., (3) Methoxy and ethoxy ** propoxy, isopropoxy, butoxy, Alkoxy ** which consists of the alkyls and the oxygen atoms of the carbon numbers 1-4 chosen from 3rd class butoxy etc. (4) Fluoro methyl, difluoromethyl, trifluoromethyl, 2-fluoro ethyl, The halo alkyl of the carbon numbers 1-4, such as 2 and 2-difluoro ethyl, 2 and 2, and 2-trifluoro ethyl, (5) Hydroxy ** (6) amino, (7) dimethylamino, diethylamino, Each has independently the alkyl of the carbon numbers 1-4 chosen from N-methyl-N-ethylamino, pyrrolidine-1-IRU, piperidine-1-IRU, etc. Dialkylamino, (8) nitroglycerine with which an alkyl part may form a ring, (9) The cyano ** (10) formyl, acetyl, a propionyl, 2-methyl propionyl, The acyl which consists of the alkyls and carbonyls of the carbon numbers 1-4 chosen from the butyryl etc., (11) A carboxylic acid, (12) methoxycarbonyls, ethoxycarbonyl, Propoxy carbonyl, isopropoxycarbonyl, butoxycarbonyl, The ester which consists of ARUKOKISHI and carbonyls of the carbon numbers 1-4 chosen from the 3rd class butoxycarbonyl etc., (13) N-alkyl carbamoyl [which consists of carbamoyl, (14) monoalkylamino or dialkylamino and carbonyl] or N, and N-dialkyl carbamoyl, (15) Acylamino or diacyl amino which consists of acyl (above and homonymy) and amino, (16) A thiol, (17) methylthios, ethyl thio, propyl thio, The alkylthio which consists of the alkyls and the sulfur atoms of the carbon numbers 1-4 chosen from butyl thio etc., (18) Alkoxycarbonylamino which consists of ester and amino, (19) N-alkyl sulfamoyl [which consists of sulfamoyl, (20) monoalkylamino or dialkylamino and a sulfone] or N, and N-dialkyl sulfamoyl, **** may be mentioned and 1-3 pieces may be preferably permuted by one or more carbon atoms of the

arbitration of Ar. Moreover, the ring may newly be formed on the carbon atom with which it adjoined on Ar at the substituents which were shown above and which adjoined the same or when a different substituent existed.

[0015] The desirable compound contained in a general formula (I) is as follows. A number shows an example number.

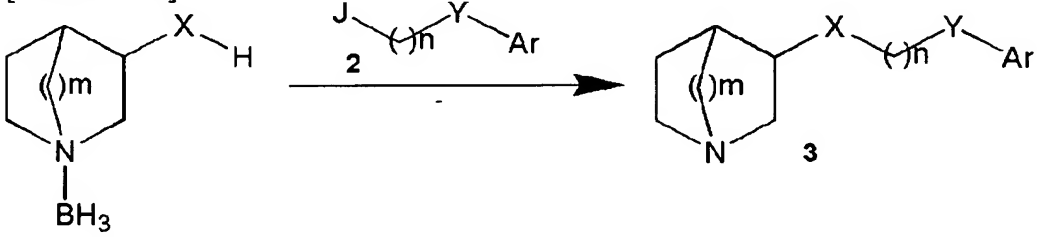
(1) 3-([Benzo b] thiophene-2-IRU) (methoxy)-1-azabicyclo [2.2.2] octane, (2) (R)-3-([Benzo b] thiophene-2-IRU) (methoxy)-1-azabicyclo [2.2.2] octane, (3) (S)-3-([Benzo b] thiophene-2-IRU) (methoxy)-1-azabicyclo [2.2.2] octane, (5) 3-(2-naphthyl) (methoxy)-1-azabicyclo [2.2.2] octane, (7) 3-(2-([Benzo b] thiophene-2-IRU) ethyl)-1-azabicyclo [2.2.2] octane, (8) (+)-3-(2-([Benzo b] thiophene-2-IRU) ethyl)-1-azabicyclo [2.2.2] octane, (9) (-)-3-(2-([Benzo b] thiophene-2-IRU) ethyl)-1-azabicyclo [2.2.2] octane, (10) 3-(2-([Benzo b] thiophene-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane, (11) (+)-3-(2-([Benzo b] thiophene-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane, (12) (-)-3-(2-([Benzo b] thiophene-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane, (13) 3-(2-(benzothiazole-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane, (15) 3-(2-([Benzo b] furan-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane.

[0016] As a salt which can be permitted on the compound of a general formula (I), and its physic, an acid addition salt with inorganic acids (a hydrochloric acid, a hydrobromic acid, a sulfuric acid, a phosphoric acid, nitric acid, etc.) or organic acids (an acetic acid, a propionic acid, a succinic acid, a glycolic acid, a lactic acid, a malic acid, a tartaric acid, a citric acid, a maleic acid, a fumaric acid, methansulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, a camphor sulfonic acid, ascorbic acid, etc.) is mentioned. Moreover, it can also consider as an oxalate for the purpose of crystallization of a compound. Since the salt which can be permitted on the compound of a general formula (I) and a hydrate, or its physic may exist in the form of a hydrate or solvate, these hydrates (1/2 hydrate, 1/3 hydrate, one hydrate, 3/2 hydrate, two hydrates, three hydrates, etc.) and solvate are also included by this invention. Moreover, when the compound of a general formula (I) has an asymmetrical atom, at least two kinds of optical isomers exist. These optical isomer and its racemic modification are included by this invention.

[0017] this invention compound contained in a general formula (I) is compoundable by the following approach. In a reaction formula, especially the definition of each notation is synonymous with the above, unless it is shown.

Synthesis method 1 [0018]

[Formula 11]

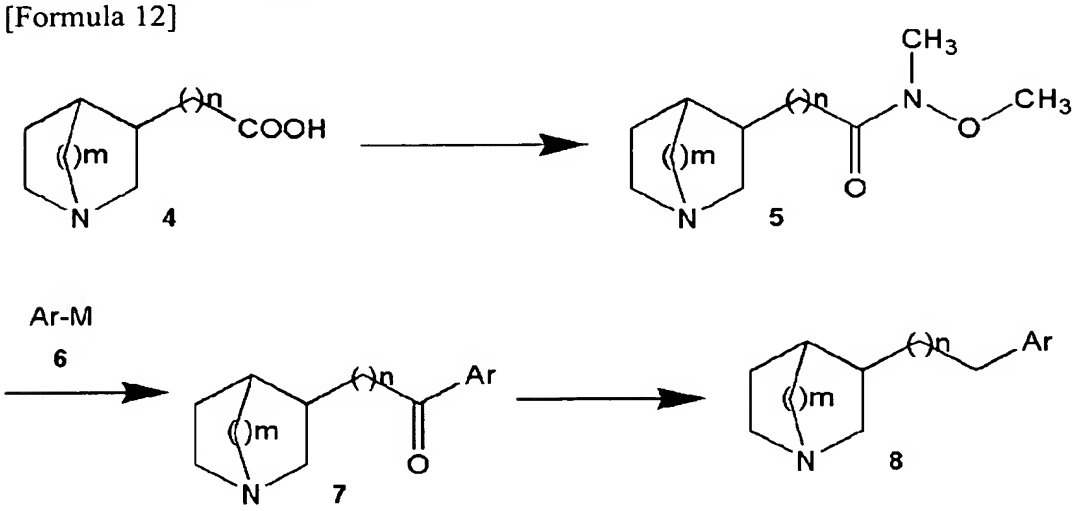


[0019] the compound of a formula (1), and the compound (the inside of a formula, and J -- a chlorine atom and a bromine atom --) of a formula (2) the suitable leaving group generally used on synthetic organic chemistry, such as an iodine atom, trifluoromethane sulfonyloxy, p-toluenesulfonyloxy, and METANSURUFONIRUOKISHI, is shown. Sodium methoxide, a sodium ethoxide, a potassium methoxide, potassium ethoxide, the 3rd class butoxide of a potassium, sodium, a potassium, potassium carbonate, A potassium hydrogencarbonate, a sodium carbonate, a sodium hydrogencarbonate, sodium acetate, potassium acetate, a sodium hydroxide, A potassium hydroxide, a sodium hydroxide, the suitable solvent (benzene, toluene, a xylene, dimethyl formamide, dimethyl sulfoxide, and a N-methyl-2-pyrrolidone --) which does not check advance of a reaction under existence of the suitable base

generally used on the synthetic organic chemistry of sodium hydride, butyl lithium, etc. Or inside, such as these mixed solvents, It can be made to be able to react at the reflux temperature of a solvent for 0.1 to 48 hours, and the compound shown in the formula (3) can be obtained from a room temperature by carrying out deprotection of the boron using suitable acids generally used on synthetic organic chemistry, such as dilute hydrochloric acid and a dilute sulfuric acid, further.

Synthesis method 2 [0020]

[Formula 12]



[0021] The compound of a formula (4), N, and O-dimethyl hydroxylamine the suitable solvent (benzene, toluene, a xylene, ethyl acetate, dimethyl formamide, dimethyl acetamido, dimethyl sulfoxide, a N-methyl-2-pyrrolidone, a methylene chloride, chloroform, an ethylene dichloride, and a tetrahydrofuran --) which does not check advance of a reaction the suitable base (triethylamine and a pyridine --) which does not check advance of a reaction into dioxane, diethylether, diisopropyl ether, or the mixed solvent of such arbitration A dimethylamino pyridine, diisopropyl ethylamine, potassium carbonate, A potassium hydrogencarbonate, a sodium carbonate, a condensing agent (cyano phosphoric-acid diethyl and benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (Bop reagent) --) suitable at the reflux temperature of -78 degrees C to the bottom of existence of a sodium hydrogencarbonate etc., and a solvent The compound shown in the formula (5) can be obtained by adding 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide (WSCI), 1, and 3-dicyclohexylcarbodiimide (DCCD) etc., and making it react for 0.1 to 48 hours. The compound of a formula (5) moreover, a compound (4) Advance of a reaction the suitable solvent (benzene, toluene, a xylene, ethyl acetate, dimethyl formamide, dimethyl acetamido, dimethyl sulfoxide, a N-methyl-2-pyrrolidone, a methylene chloride, chloroform, and an ethylene dichloride --) which is not checked or the suitable base (triethylamine and a pyridine --) which does not check advance of a reaction into the mixed solvent of such arbitration etc. A dimethylamino pyridine, diisopropyl ethylamine, potassium carbonate, A potassium hydrogencarbonate, a sodium carbonate, Under existence of a sodium hydrogencarbonate etc., - By adding N and O-dimethyl hydroxylamine to the mixed acid anhydride which added and generated suitable acid chlorides (chlorination pivaloyl, chloro carbonic acid isobutyl, chloro ethyl carbonate, etc.) at 20 degrees C - 10 degrees C, and making it react to it at the reflux temperature of 0 degree C - a solvent for 0.1 to 48 hours ****** -- things are made. A reactant intermediate product can be obtained using a halogenating agent [with the still more suitable compound of a formula (5) / for a compound (4)] (phosphorus oxychloride, phosphorus-pentachloride, thionyl chloride, phosphorus tribromide, phosphorus pentabromide, thionyl bromide, etc.) or 1, and 1'-carbonyl bis--1H-imidazole etc., and also making this reactant intermediate product, N, and O-dimethyl hydroxylamine react can obtain.

[0022] The compound of a formula (7) can be obtained by making the compound (M expressing metals, such as a lithium, magnesium chloride, and magnesium bromide, among a formula) of a formula (6), and

the compound of a formula (5) react among the solvent which does not bar advance of a reaction for 0.1 to 24 hours at the reflux temperature of -78 degrees C - solvents (diethylether, diisopropyl ether, a tetrahydrofuran, 1,4-dioxane, or these mixed solvents). The compound of a formula (8) can be obtained by adding the triethyl silane in trifluoroacetic acid and making the compound of a formula (7) react at the reflux temperature of 0 degree C - a solvent for 0.1 to 24 hours. Moreover, the compound of a formula (7) can once be in the compound of a formula (8) with suitable reducing agents, such as a sodium borohydride, lithium hydride aluminum, and diisobutyl aluminum hydroxide, the alcoholic body can be acquired, and dissolving this alcoholic object in an acetonitrile, adding a sodium iodide and a chloro trimethyl silane, and also making it react at the reflux temperature of 0 degree C - a solvent for 0.1 to 24 hours can obtain.

[0023] Thus, isolation purification of this invention compound obtained can be carried out with conventional methods, such as the recrystallizing method and the column chromatography method. the time of the product obtained being racemic modification -- for example, judgment recrystallization of a salt with an optical activity acid -- or it can divide into the desired optically active substance by letting the column filled up with optical activity support pass. Each diastereomer is separable with means, such as fractional-crystallization-izing and a chromatography. These are obtained also by using an optical activity raw material compound etc. Moreover, a stereoisomer can be isolated by the recrystallizing method, the column chromatography method, etc.

[0024] When the salt which can be permitted on 1-azabicyclo alkane compound of this invention, its optical isomer, or its physic is used as physic, the support (an excipient, a binder, disintegrator, and corrigent --) which can permit this invention compound on pharmaceutical preparation the physic constituent which is mixed with an odor-masking agent, an emulsifier, a diluent, a solubilizing agent, etc., and is obtained, or pharmaceutical preparation (a tablet --) A medicine can be prescribed for the patient taking-orally-wise or parenterally with gestalten, such as a pill agent, a capsule, a granule, powder, syrups, an emulsion agent, elixirs, suspension, a solution agent, injections, drops, or suppositories. A physic constituent can be pharmaceutical-preparation-ized according to the usual approach. In this specification, subcutaneous injection, an intravenous injection, an intramuscular injection, intraperitoneal injection, or a spot method is included as it is parenteral. Dispensing for injection, for example, a sterile water-for-injection nature suspended solid, and an oily suspended solid can be prepared by the suitable decentralization agent or the approach which was damp and was learned for the field concerned using ** and a suspending agent. the dispensing for sterile injection -- moreover -- for example, you may be the solution or suspension which can perform sterile injection in the nontoxic diluent of a water solution etc. which can carry out parenteral administration, or a solvent. As what is allowed as the vehicle which can be used, or a solvent, water, Ringer's solution, an isotonic sodium chloride solution, etc. are raised. Furthermore, fixed oil sterile as a solvent or a slurrying solvent can also usually be used. For that, any fixed oil and a fatty acid can be used and the monochrome, JI, or the triglycerides of the fatty oil of nature, composition, or a semisynthesis or a fatty acid and nature, composition, or a semisynthesis is also included.

[0025] Although they are solid-states in ordinary temperature, such as the drug and a suitable non-stimulative ** form agent, for example, cocoa butter and polyethylene glycols, at the temperature of an intestinal tract, it is a liquid, and the suppositories for rectum administration are dissolved within the rectum, they can be mixed with what emits a drug and can be manufactured. As a solid administration pharmaceutical form for internal use, the above-mentioned things, such as powder material, a granule, a tablet, a pill agent, and a capsule, are raised. In such a pharmaceutical form, an active-ingredient compound is mixable with the polymers of at least one additive, for example, cane sugar, a lactose, cellulose sugar, mannitol, maltitol, a dextran, starches, an agar, alginate, chitins, chitosan, pectin, tragacanth gums, gum arabic, gelatin, collagens, casein, albumin, composition, or a semisynthesis, or glycerides. Such a pharmaceutical form object can contain the further additive like usual again, for example, anti-oxidants, such as preservatives, such as lubricant, such as an inactive diluent and magnesium stearate, paraben, and sorbins, an ascorbic acid, alpha-tocopherol, and a cysteine, disintegrator, a binder, a thickener, a buffer, a sweet taste grant agent, a flavor grant agent, a par fumes

agent, etc. are raised. Enteric coating of a tablet and the pill agent can be carried out further, and they can also be manufactured. The emulsion agent by which the liquids and solutions for internal use are permitted as physic, syrups, elixirs, suspension, a solution agent, etc. are raised, and they may contain the inactive diluent usually used in the field concerned, for example, water.

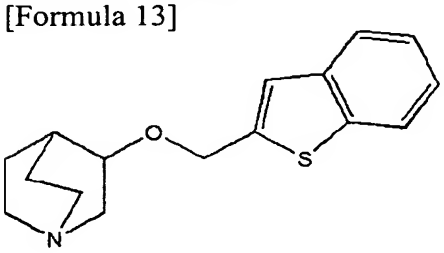
[0026] The salt which can be permitted on the compound of a general formula (I), an optical isomer, or its physic has alternative and powerful alpha7 nicotinic-receptor actuation operation or alpha7 nicotinic-receptor partial actuation operation, and is effective in remedies, such as an Alzheimer disease, cognitive dysfunction, an attention deficit hyperactivity disorder, anxiety, depression, schizophrenia, epilepsy, a pain, tow let syndrome, a Parkinson Mr. disease, and a Huntington disease, or a prophylactic, the remedy of a neurodegenerative disease with which cholinergic nerve transfer has caused abnormalities or a prophylactic, and a pan as a non-smoking medicine. A dose is decided in consideration of the factor of them or others according to age, weight, general health condition, sex, a meal, administration time amount, a medication method, an elimination rate, the combination of a drug, and extent of the condition of disease which is treating then [patient]. Although the salt which can be permitted on this invention compound, its optical isomer, or its physic can be used for insurance by low toxicity and the dose on the 1st changes with a patient's condition, weight and the class of compound, routes of administration, etc. for example, -- parenteral -- the inside of the inside of hypodermically and a vein, intramuscular, or the rectum -- about 0.01 -- a -50mg/person/day -- desirable -- a 0.01-20mg/person/day -- a medicine is prescribed for the patient -- having -- moreover, taking orally ---like -- about 0.01 -- a -150mg/person/day -- desirable -- a 0.1-100mg/person/day -- it is desirable to prescribe a medicine for the patient. Moreover, this compound which has alternative and powerful compatibility to alpha7 nicotinic receptor is useful to the compound for indicators of alpha7 nicotinic receptor within a brain etc. as ligand of alpha7 nicotinic receptor.

[0027]

[Example] Hereafter, although an example, the example of a pharmaceutical preparation formula, and the example of an experiment explain this invention to a detail, this invention is not limited at all by these.

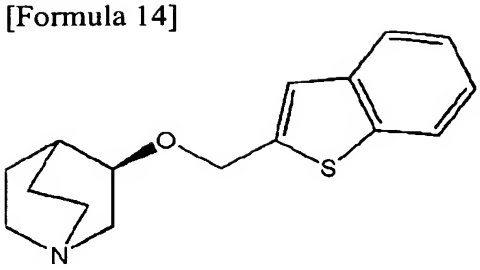
Example 1 [0028]

[Formula 13]



[0029] 0.5g of 1-azabicyclo [2.2.2] octane-3-all-borane complexes was dissolved in dimethylformamide 5ml, and under ice-cooling, 0.17g (60%) of sodium hydride was added, and it stirred for 30 minutes. 2-chloro methyl [benzo b] thiophene 0.77g was added to reaction mixture, and it stirred for further 1 hour. Reaction mixture was opened in iced water after reaction termination, ethyl acetate extracted, and it dried with the sodium sulfate. The residue which condensed the solvent and was obtained was given to the silica gel chromatography, a part for hexane:ethyl-acetate =9:1 outflow was condensed, and 0.3g of 3-([Benzo b] thiophene-2-IRU) (methoxy)-1-azabicyclo [2.2.2] octane-borane complexes was obtained. This compound was dissolved in acetone 10ml, 3 convention hydrochloric acid was added under ice-cooling, and it stirred at the room temperature for 1 hour. After reaction termination, water was added to the residue which condensed the solvent and was obtained, ethyl acetate extracted, and it dried with the sodium sulfate. The residue which condensed the solvent and was obtained was dissolved in ethyl acetate, the crystal which added the hydrochloric-acid-ether and deposited was separated, and 0.17g of 3-([Benzo b] thiophene-2-IRU) (methoxy)-1-azabicyclo [2.2.2] octane hydrochloride and 1/2 hydrates was obtained. Melting point 201-203 degree-C example 2 [0030]

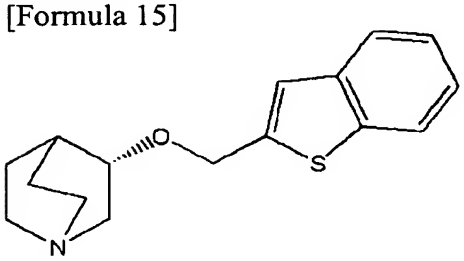
[Formula 14]



[0031] (R) It was made to react like an example 1 using 0.065g of -1-azabicyclo [2.2.2] octane-3-all-borane complexes, and 0.021g of (R)-3-([Benzo b] thiophene-2-IRU) (methoxy)-1-azabicyclo [2.2.2] octane hydrochlorides was obtained. Melting point 211-212 degree-C.[alpha] D=-52 degree (c= 0.23, MeOH)

Example 3 [0032]

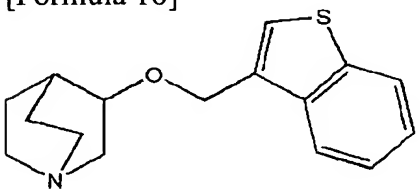
[Formula 15]



[0033] (S) It was made to react like an example 1 using 0.37g of -1-azabicyclo [2.2.2] octane-3-all-borane complexes, and 0.061g of (S)-3-([Benzo b] thiophene-2-IRU) (methoxy)-1-azabicyclo [2.2.2] octane hydrochlorides was obtained. Melting point 211-213 degree-C. [alpha] D= +56 degrees (c= 0.25, MeOH)

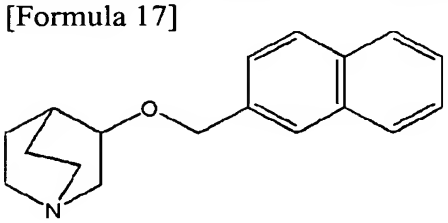
Example 4 [0034]

[Formula 16]



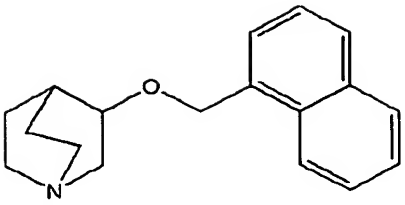
[0035] It was made to react like an example 1 using 3-chloro methyl [benzo b] thiophene 0.77g, and 0.155g of 3-([Benzo b] thiophene-3-IRU) (methoxy)-1-azabicyclo [2.2.2] octane hydrochloride and 3/2 hydrates was obtained. Melting point 153-156 degree-C example 5 [0036]

[Formula 17]

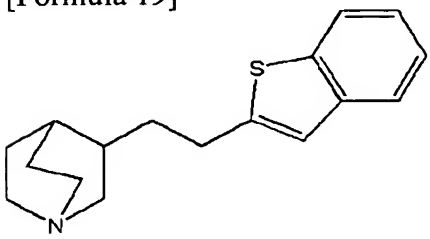


[0037] It was made to react like an example 1 using 2-chloro methylnaphthalene 0.74g, and a 3-(2-naphthyl) (methoxy)-1-azabicyclo [2.2.2] octane hydrochloride and 0.103g of 1 hydrates were obtained. Melting point 187-189 degree-C example 6 [0038]

[Formula 18]

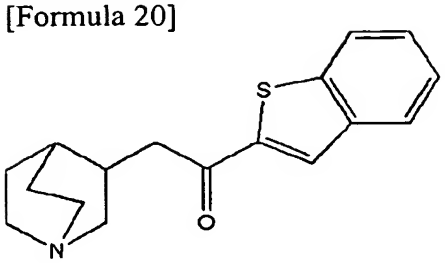


[0039] It was made to react like an example 1 using 1-chloro methylnaphthalene 0.74g, and 0.1g of 3-(1-naphthyl) (methoxy)-1-azabicyclo [2.2.2] octane hydrochlorides was obtained. Melting point 191-194 degree-C example 7 [0040]
[Formula 19]

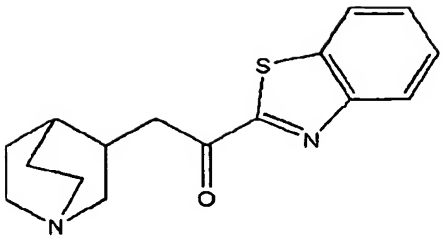


[0041] 3-(2-([Benzo b] thiophene-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane 1.2g was dissolved in 10ml of trifluoroacetic acid, triethyl silane 1.7ml was added, and it stirred for five days at the room temperature. The system of reaction was diluted with 30ml of water, it was made alkalinity by the sodium carbonate, and chloroform extracted the specified substance 3 times. The residue which dried the organic layer with the sodium sulfate, and was condensed and obtained was given to the silica gel column chromatography, and a part for 7:3 to hexane:ethyl-acetate =6:4 outflow was condensed. Residue was dissolved in the acetone, the hydrochloric-acid methanol was added 32%, the hydrochloride was adjusted, the solvent was distilled off under reduced pressure, the crystal which added isopropanol and deposited was separated, and 0.105g of 3-(2-([Benzo b] thiophene-2-IRU) ethyl)-1-azabicyclo [2.2.2] octane hydrochloride and 1/4 hydrates was obtained. The 218 to 220 degree C melting point [0042] Example 8(+)-3-(2-([Benzo b] thiophene-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane 0.28g was dissolved in methanol 10ml, and under ice-cooling, 0.038g of sodium borohydrides was added and it stirred at the room temperature. The saturation sodium-carbonate water solution was added to the system of reaction after reaction termination, and chloroform extracted the product twice. The organic layer was dried with anhydrous sodium sulfate, the residue obtained by distilling off a solvent under reduced pressure was given to the silica gel column chromatography, and 0.13g of alcoholic bodies was acquired. 0.4g of sodium iodides was dissolved in acetonitrile 5ml, chloro trimethyl silane 0.34ml was added under ice-cooling, and it stirred for 30 minutes at the room temperature. At the room temperature, 0.13g of alcoholic bodies was added to the suspension of the yellow to produce, and it stirred for 30 minutes at the room temperature. The sodium sulfite water solution was added after reaction termination, and, subsequently to alkalinity, it carried out with saturation sodium-carbonate water. Chloroform extracted the product twice, the residue obtained in the organic layer by distilling off after desiccation and a solvent under reduced pressure with anhydrous sodium sulfate was given to the silica gel column chromatography, and oily matter was obtained. Oily matter was dissolved in isopropanol, the crystal which added the 32% hydrochloric-acid-methanol and was produced was separated, and 0.060g of (+)-3-(2-([Benzo b] thiophene-2-IRU) ethyl)-1-azabicyclo [2.2.2] octane hydrochloride and 1/4 hydrates was obtained. The 248 to 250 degree C melting point, [alpha] D=+41.2 degree (c= 0.25, MeOH)
[0043] It was made to react like an example 8 using example 9(-)-3-(2-([Benzo b] thiophene-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane 0.31g, and 0.015g of (-)-3-(2-([Benzo b] thiophene-2-IRU) ethyl)-1-azabicyclo [2.2.2] octane hydrochlorides was obtained. The 228 to 232 degree C melting point, [alpha] D=-36.4 degree (c= 0.25, MeOH)

Example 10 [0044]
[Formula 20]

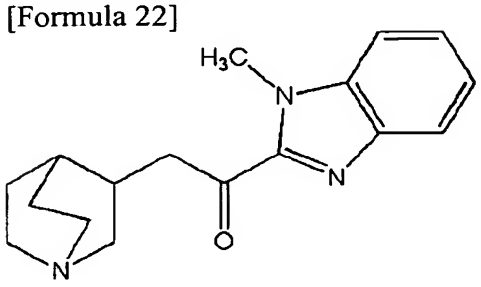


[0045] [Benzo b] thiophene 0.76g was dissolved in tetrahydrofuran 10ml, and under nitrogen-gas-atmosphere mind, at -78 degrees C, 3.5ml of hexane solutions of 1.6 convention n-butyl lithium was added, and it stirred for 10 minutes. 5ml of N-methyl-N-methoxy-2-(1-azabicyclo [2.2.2] octane-3-IRU) acetamido 1.0g tetrahydrofuran solutions was dropped here, and it stirred for 15 minutes at -78 degrees C. After reaction termination, water was added to reaction mixture and chloroform extracted twice. The organic layer was dried with the sodium sulfate, the residue which condensed the solvent and was obtained was given to the silica gel column chromatography, a part for a chloroform outflow was condensed, and oily matter was obtained. The obtained oily matter was dissolved in isopropyl alcohol, the crystal which added the 32% hydrochloric-acid-methanol and deposited was separated, and 0.23g of 3-(2-([Benzo b] thiophene-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane hydrochlorides was obtained. The 247 to 249 degree C melting point [0046] 20ml of ** ethanol solutions of 1.3g of L-malic acid is added to 30ml of example 113-(2-([Benzo b] thiophene-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane 2.9g ** ethanol solutions. The solution was returned to the room temperature and the crystal which deposits was separated. It recrystallized 3 times using ethanol-water in 3.5g of obtained crystals, and 0.72g of L-malic acid salts of (+)-3-(2-([Benzo b] thiophene-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane was obtained. Add a saturation sodium-carbonate water solution to the obtained malate, chloroform extracts the specified substance twice, and an organic layer is dried with anhydrous sodium sulfate. The crystal which condensed the solvent and was obtained is dissolved in a methanol. The crystal which added the hydrochloric-acid-methanol and deposited was separated and 0.28g of (+)-3-(2-([Benzo b] thiophene-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane hydrochloride and 1/5 hydrates was obtained. The 226 to 227 degree C melting point, [alpha] D=-36.2 degree (c= 0.25, MeOH)
[0047] The filtrate produced in the example 12 example 11 was mixed, the saturation sodium-carbonate water solution was added to the residue obtained by distilling off a solvent under reduced pressure, and chloroform extracted. After drying an organic layer with anhydrous sodium sulfate, the crystal which adds 5ml of ** ethanol solutions of 0.54g of D-malic acids to 10ml of ** ethanol solutions of 1.15g of residue which condensed the solvent and was obtained, and deposits was separated. Recrystallization was performed for the obtained crystal 3 times using ethanol-water, and D-malate of --3-(2-([Benzo b] thiophene-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane was obtained. The saturation sodium-carbonate water solution was added to the obtained malate, chloroform extracted the specified substance twice, the organic layer was dried with anhydrous sodium sulfate, the crystal which condensed the solvent and was obtained was dissolved in the methanol, the crystal which added the hydrochloric-acid-methanol and deposited was separated, and 0.28g of (-)-3-(2-([Benzo b] thiophene-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane hydrochlorides was obtained. The 230 to 232 degree C melting point, [alpha] D=-36.0 degree (c= 0.25, MeOH)
Example 13 [0048]
[Formula 21]



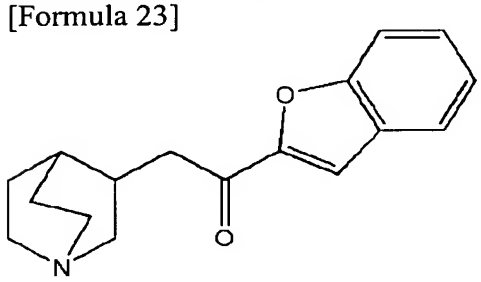
[0049] It reacted like the example 10 using benzothiazole 2.23g and N-methyl-N-methoxy-2-(1-azabicyclo [2.2.2] octane-3-IRU) acetamido 1.0g, and 0.24g of 3-(2-(benzothiazole-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane hydrochlorides was obtained. Melting point 274-275 degree-C example 14 [0050]

[Formula 22]



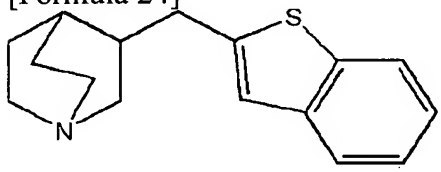
[0051] It reacted like the example 10 using 1-methyl benzimidazole 2.2g and N-methyl-N-methoxy-2-(1-azabicyclo [2.2.2] octane-3-IRU) acetamido 1.0g, and 0.6g of 3-(2-(1-methyl benzimidazole-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane 3 hydrochlorides was obtained. Melting point 246-247 degree-C example 15 [0052]

[Formula 23]



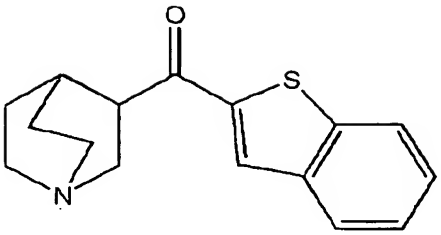
[0053] It reacted like the example 10 using benzo [b] furan 1.95g and N-methyl-N-methoxy-2-(1-azabicyclo [2.2.2] octane-3-IRU) acetamido 1.0g, and 0.6g of 3-(2-([Benzo b] furan-2-IRU)-2-oxo-ethyl)-1-azabicyclo [2.2.2] octane hydrochloride and 1/5 hydrates was obtained. Melting point 288-290 degree-C example 16 [0054]

[Formula 24]



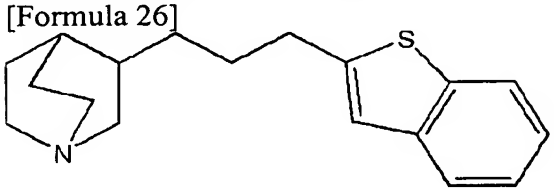
[0055] It was made to react like an example 8 using 3-([Benzo b] thiophene-2-IRU) (carbonyl)-1-azabicyclo [2.2.2] octane 1.0g, and the 3-([Benzo b] thiophene-2-IRU) (methyl)-1-azabicyclo [2.2.2] octane hydrochloride was obtained. Melting point 264-265 degree-C example 17 [0056]

[Formula 25]



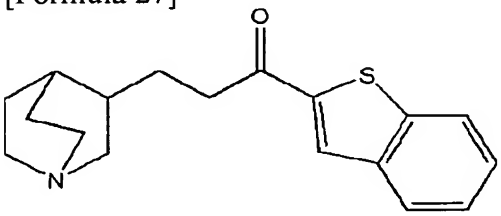
[0057] It was made to react like an example 10 using benzothiophene 5.4g and N-methyl-N-methoxy-2-(1-azabicyclo [2.2.2] octane-3-IRU) carboxamide 2.0g, and 3-([Benzo b] thiophene-2-IRU) (carbonyl)-1-azabicyclo [2.2.2] octane hydrochloride and 1/5 hydrate 1.0gg was obtained. Melting point 236-238 degree-C example 18 [0058]

[Formula 26]



[0059] It was made to react like an example 8 using 3-(3-([Benzo b] thiophene-2-IRU)-3-oxo-propyl)-1-azabicyclo [2.2.2] octane 1.0g, and 0.146g of 3-(3-([Benzo b] thiophene-2-IRU) propyl)-1-azabicyclo [2.2.2] octane hydrochloride and 1/4 hydrates was obtained. Melting point 176-178 degree-C example 19 [0060]

[Formula 27]



[0061] Benzothiophene 2.93g, N - It was made to react like an example 10 using methyl-N-methoxy-3-(1-azabicyclo [2.2.2] octane-3-IRU) propane amide 1.65g, and 1.6g of 3-(3-([Benzo b] thiophene-2-IRU)-3-oxo-propyl)-1-azabicyclo [2.2.2] octane hydrochloride 1/5 hydrates was obtained. The 280 to 282 degree C melting point [0062] After mixing with the compound 0.5 section of example of pharmaceutical preparation formula 1 example 1, the lactose 25 section, the crystalline cellulose 35 section, and the corn-starch 3 section well, it often kneaded with the binder which **(ed) in the corn-starch 2 section. Screening of this kneaded object is carried out by 16 meshes, and screening is carried out by 24 meshes after desiccation at 50 degrees C among oven. After often mixing the kneading fine-particles [which were obtained here] and corn-starch 8 section, the crystalline cellulose 11 section, and the talc 9 section, squeezing tableting is carried out and the tablet of 0.5mg content of active principles per one lock is obtained.

[0063] 1.0mg of compounds and 9.0mg of sodium chlorides of example of pharmaceutical preparation formula 2 example 1 are dissolved and filtered with water for injection, pyrogen is removed, filtrate is moved to the bottom of sterile at ampul, and 1.0mg content injections of active principles are obtained by carrying out melting seal after sterilization.

[0064] The pharmacological activity which was excellent in the compound of a general formula (I) is proved by a series of trials shown below.

Example [of an Experiment] 1: Compatibility over alpha7 nicotinic receptor ([125I] alpha bungarotoxin association)

It homogenizes with the cane-sugar solution of 0.32M with which the amount cooled the rat

hippocampus 15 times, and centrifugal separation is carried out for 10 minutes (4 degrees C) by 1,000G. Supernatant liquid is taken, centrifugal separation is carried out for 20 minutes (4 degrees C) by 20,000G, it homogenizes with distilled water which cooled dregs, and centrifugal separation is carried out for 20 minutes (4 degrees C) by 8,000G. After carrying out centrifugal separation of this supernatant liquid for 20 minutes (4 degrees C) by 40,000G, a pellet is again homogenized with cooled distilled water, and carries out centrifugal separation for 20 minutes (4 degrees C) by 40,000G. The last sediment is kept to a freezer (-80 degrees C). It suspends with the buffer solution (a 118mM sodium chloride water solution, a 4.8mM potassium chloride water solution, a 2.5mM calcium chloride water solution, a 1.2mM magnesium sulfate mixture solution, a 20mM Na-HEPES buffer, pH7.5) which cooled dregs, and the film preparation of a hippocampus is prepared at joint trial that day. a previous report (Briggs CA et al. --) Functional characterization of the novel neural nicotinic acetylcholine receptor ligand GTS-21 in vitro and in vivo.Pharmacolo.Biochem.Behav.57 (1/2) : The approach of 231-241 and 1997 is followed. [125I] alpha bungarotoxin (>7.4 TBq/mmol, IM-109, and Amersham), A hippocampus film preparation, the buffer solution (a 118mM sodium chloride water solution, a 4.8mM potassium chloride water solution, a 2.5mM calcium chloride water solution, a 1.2mM magnesium sulfate mixture solution, 20 mMNa-HEPES buffer, pH7.5), The incubation of the trial compound is carried out at 37 degrees C for 3 hours. The buffer solution which carried out suction filtration and which was quickly cooled using the cell harvester (Blanc Dale) on the Watt Mann GF/B filter (it pretreats in 0.5% polyethyleneimine water solution of bovine-serum-albumin content 0.1% for at least 3 hours) washes a reaction 3 times. The activity (125I) combined with the filter is measured at a gamma counter. Moreover, nonspecific association is 1microM. It asks under existence of alpha bungarotoxin (Wako Pure Chem, Inc.) or 100microM(-)-nicotine (Research Biochemicals Int., USA). Specific bindings were 50-70% of all association. IC50 value of this invention compound and a contrast compound is shown below as a result of an exam. A compound number shows an example number. Comparison compounds are the following compound A and B.

Comparison compound A: AR-R 17779 (WO 96/06098)

Comparison Compound B: 3-benzyloxy-1-azabicyclo [2.2.2] Octane (compound 2 of JP,4-226981,A)

[0065]

[Table 1]

化合物番号	[^{125}I] αブンガロトキシン結合 IC_{50} (nM)
1	59
3	26
5	150
7	26
8	65
9	22
10	150
11	130
12	170
13	70
15	97
16	110
比較化合物A	680
比較化合物B	3700

[0066] Example [of an Experiment] 2: Compatibility over alpha4beta2 nicotinic receptor ([3H] Cytisine association)

It homogenizes with the cane-sugar solution of 0.32M with which the amount cooled the rat cerebral cortex 15 times, and centrifugal separation is carried out for 10 minutes (4 degrees C) by 1,000G.

Supernatant liquid is taken, centrifugal separation is carried out for 20 minutes (4 degrees C) by 20,000G, it homogenizes with distilled water which cooled dregs, and centrifugal separation is carried out for 20 minutes (4 degrees C) by 8,000G. After carrying out centrifugal separation of this supernatant liquid for 20 minutes (4 degrees C) by 40,000G, a pellet is again homogenized with cooled distilled water, and carries out centrifugal separation for 20 minutes (4 degrees C) by 40,000G. The last dregs are kept to a freezer (-80 degrees C). It suspends with the buffer solution (a 120mM sodium chloride water solution, 5mM potassium chloride water solution, a 2.5mM calcium chloride water solution, 1mM magnesium sulfate mixture solution, a 50mM tris-hydrochloric-acid buffer, pH7.4) which cooled dregs, and the film preparation of the cerebral cortex is prepared at joint trial that day.

[0067] [3H] Carry out the incubation of Cytisine (555GBq-1.48 TBq/mmol, NET-1054, NEN Life Science Products, USA), a cerebral cortex film preparation, the buffer solution (a 120mM sodium chloride water solution, 5mM potassium chloride water solution, a 2.5mM calcium chloride water solution, 1mM magnesium sulfate mixture solution, a 50mM tris-hydrochloric-acid buffer, pH7.4), and the trial compound for 75 minutes at 4 degrees C. The buffer solution which carried out suction filtration and which was quickly cooled using the Blanc Dale cell harvester on the Watt Mann GF/B filter (it pretreats in 0.5% polyethyleneimine water solution of bovine-serum-albumin content 0.1% for at least 3 hours) washes a reaction 3 times. After putting a filter into a vial bottle and adding a liquid scintillator, the activity (tritium) combined with the filter is measured with a liquid scintillation counter. A liquid scintillator is added and activity (tritium) is measured with a liquid scintillation counter. Moreover, it asks for nonspecific association under existence of 10microM(-)-nicotine (Research Biochemicals Int., USA). Specific bindings were 80% or more of all association. As a result of the exam, IC50 value of this invention compound was 1000 or more nMs, and the compatibility over alpha4beta2 nicotinic receptor was very weak. That is, this invention compound is a compound which has alternative compatibility in alpha7 nicotinic receptor.

[0068] Example [of an Experiment] 3: Agonist activity over alpha7 nicotinic receptor (electrophysiology trial in PC12 cell)

. nystatin punching patch clamping which performed electrophysiology-measurement after carrying out seeding of the PC12 cell (it purchases from Dainippon Pharmaceutical Co., Ltd.) to 35mm two culture plates which carried out the collagen coat and cultivating it on one to the 3rd () [Akaike N.and] PC12 cell by Harata N., Jap.J.Physiol., 44 volumes, 433 - 473 pages, and 1994 under the conditions which carried out membrane potential immobilization (VH=-70mV) At the outside liquid moment, with an exchange buffering method (Y-tube law, Murase et al., and Brain Res. 525 volumes, 84 -91 pages, 1990) The extracellular fluid used for . measurement which prescribed test compound liquid (it dissolves in extracellular fluid) for the patient, and measured the amplitude of the transient inward current (alpha7 acceptor response) caused, and the liquid in a pipet are the following presentations.

Extracellular fluid: A 135mM sodium chloride, 2mM potassium chloride, 1mM magnesium chloride, 5mM calcium chloride, 10mM glucose, 12mM HEPES was added and it adjusted to pH=7.4 by the tris buffer.

Liquid in a pipet: What added 1% nystatin methanol solution of 1/25 amount to the 150mM cesium chloride and the solution which added 10mM HEPES and was adjusted to pH=7.2 by the tris buffer was used as the liquid in a pipet. Software (pCLAMP software ver.6, Axon Instruments) performed analysis of a current response, and the peak value of the transient inward current through alpha7 nicotinic receptor was measured for every cell. The magnitude of a test compound response was expressed with the percentage for the relative comparison with a control drug, having used as 100% magnitude of the choline 10mM response which is the alpha7 nicotinic-receptor all agonist in the same cell. Consequently, the compound 11 showed partial agonist activity to alpha7 nicotinic receptor like drawing 1 .

[0069]

[Effect of the Invention] The salt which can be permitted on the compound of a general formula (I), an optical isomer, or its physic has alternative and powerful alpha7 nicotinic-receptor actuation operation or alpha7 nicotinic-receptor partial actuation operation, and is effective in remedies, such as an Alzheimer

disease, cognitive dysfunction, an attention deficit hyperactivity disorder, anxiety, depression, schizophrenia, epilepsy, a pain, tow let syndrome, a Parkinson Mr. disease, and a Huntington disease, or a prophylactic, the remedy of a neurodegenerative disease with which cholinergic nerve transfer has caused abnormalities or a prophylactic, and a pan as a non-smoking medicine. Moreover, this invention compound is excellent in oral absorbency and brain internal transmigration nature, and has the property good as central nervous system physic.

[Translation done.]

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2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

TECHNICAL FIELD

[Field of the Invention] This invention relates to the new 1-azabicyclo alkane compound for providing the disease of a central nervous system with useful physic.

[Translation done.]

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EFFECT OF THE INVENTION

[Effect of the Invention] The salt which can be permitted on the compound of a general formula (I), an optical isomer, or its physic has alternative and powerful alpha7 nicotinic-receptor actuation operation or alpha7 nicotinic-receptor partial actuation operation, and is effective in remedies, such as an Alzheimer disease, cognitive dysfunction, an attention deficit hyperactivity disorder, anxiety, depression, schizophrenia, epilepsy, a pain, tow let syndrome, a Parkinson Mr. disease, and a Huntington disease, or a prophylactic, the remedy of a neurodegenerative disease with which cholinergic nerve transfer has caused abnormalities or a prophylactic, and a pan as a non-smoking medicine. Moreover, this invention compound is excellent in oral absorbency and brain internal transmigration nature, and has the property good as central nervous system physic.

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TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] This invention has powerful alpha7 nicotinic-receptor actuation operation or alpha7 nicotinic-receptor partial actuation operation, and it is in offering remedies, such as an Alzheimer disease, cognitive dysfunction, an attention deficit hyperactivity disorder, anxiety, depression, schizophrenia, epilepsy, a pain, tow let syndrome, a Parkinson Mr. disease, and a Huntington disease, or a prophylactic, the remedy of a neurodegenerative disease with which cholinergic nerve transfer has caused abnormalities or a prophylactic, and the still more useful new molecular entity as a non-smoking medicine.

[Translation done.]